Journal of Surgical Oncology 2000;73:134–137

Variation in Axillary Node Dissection Influences the Degree of Nodal Involvement in Breast Cancer Patients

SANJOY SAHA, MD,[1] WILLIAM B. FARRAR, MD,[1] DONN C. YOUNG, PhD,[2]
JOHN J. FERRARA, MD,[3] WILLIAM E. BURAK, JR., MD[1]*

[1]*Division of Surgical Oncology, Department of Surgery, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Ohio State University, Columbus, Ohio*
[2]*Division of Biostatistics, Arthur G. James Cancer Hospital and Richard Solove Research Institute, Ohio State University, Columbus, Ohio*
[3]*Department of Surgery, Henry Ford Hospital, Detroit, Michigan*

Background and Objectives: The number of positive axillary lymph nodes predicts prognosis and is often important in determining adjuvant chemotherapy in breast cancer patients. This study was undertaken to determine if differences in the extent of axillary node dissection would alter the number of reported positive nodes.

Methods: The study population consisted of 302 patients with invasive breast cancer who underwent complete (level I/II/III) axillary lymph node dissection. Assuming that all patients had undergone a level I/II dissection, it was determined how frequently a patient's nodal category (0, 1–3, 4–9, >10 positive nodes) would have been altered if a level I or level I/II/III dissection were performed.

Results: Assuming that all 302 patients had undergone a level I/II dissection, performing only level I dissection would have resulted in a change in nodal category in 15.9% of all patients and 36.1% of patients with positive nodes. The corresponding changes for a level I/II/III dissection would have been 4.3% and 9.5%, respectively.

Conclusions: Variations in the level of axillary node dissection for breast cancer can result in significant changes in the number of positive axillary nodes. This can potentially bias adjuvant chemotherapy recommendations if treatment decisions are based on this prognostic factor.

J. Surg. Oncol. 2000;73:134–137.

KEY WORDS: **breast cancer; lymph nodes; axillary level; axillary dissection; metastasis**

INTRODUCTION

Axillary dissection remains an important staging procedure in patients with early breast cancer. While the therapeutic value of axillary dissection is debatable, the status of the lymph nodes is the single most important prognostic factor with regard to recurrence and survival [1]. Decisions concerning adjuvant chemotherapy have traditionally been based on primary tumor size and the presence or absence of lymph node metastases. While a poorer prognosis is seen with nodal involvement, the number of metastatic nodes has also been shown to influence disease-free and overall survival [2]. More recently, there has been a trend toward treating patients based on the number of involved nodes; i.e., premenopausal patients with 10 or more positive nodes are often considered for dose-intensive chemotherapy with autologous bone marrow transplant or peripheral stem cell support [3]. The National Comprehensive Cancer Network (NCCN) has recently published practice guidelines, which include the number of positive nodes in the

*Correspondence to: William E. Burak, Jr., MD, Department of Surgery, N 908 Doan Hall, 410 West 10th Avenue, Columbus, OH 43210-1228. Fax: 614-293-3465. E-mail: burak-1@medctr.osu.edu

Accepted 21 December 1999

algorithm determining adjuvant treatment [4]. Additionally, intergroup protocols addressing dose intensification and second-line agents have used the number of positive nodes as an entry criterion. Variations in breast cancer treatment based solely on the number of positive nodes have several potential drawbacks. Differences in the methods of histological analyses of lymph nodes can lead to inconsistencies in reporting micrometastases [5]. More importantly, the number of lymph nodes presented to the pathologist varies greatly not only among different patients but also among surgeons performing this procedure. Variations in the "extent" of axillary dissection may contribute to these differences.

The axilla is divided into 3 levels based on the pectoralis minor muscle. Although the National Cancer Institute has recommended that a level I/II dissection should be standard practice, level I dissections are still performed. Moreover, level I/II/III dissections continue to be carried out in selected patients, particularly in those with grossly positive nodes [6]. Clearly, this difference in practice leads to discrepancies when axillary staging is based on the number of metastatic nodes. Up to this point, there has been a lack of data comparing a level I or I/II dissection with complete dissection (I/II/III) in establishing the number of positive nodes [7].

This retrospective study illustrates how variations in the technique and extent of axillary lymph node dissection can influence the number of reported positive nodes.

MATERIALS AND METHODS

The study population consists of patients who were enrolled in 2 institutional trials from 1984 to 1993, where information concerning the level of axillary node dissection was recorded prospectively [8,9]. Informed consent was obtained from all patients. These patients underwent either modified radical mastectomy or lumpectomy with axillary node dissection, and all had a level I/II/III dissection, which was standard practice at these institutions during that time period.

During axillary dissection, the lower axillary contents (level I/II lymph nodes) were resected en bloc with excision of the pectoralis minor muscle. Level III lymph nodes were excised separately and submitted as an additional specimen. In pathology, nodes were categorized by level: level I was lateral and inferior to the pectoralis minor muscle, level II was posterior to the pectoralis minor muscle, and level III was medial and superior to the pectoralis minor muscle. The axillary contents were processed using standard techniques (no fat clearing); routine histopathological (hematoxylin and eosin staining) analysis was performed on 1 section of each lymph node. Patients were grouped according to the number of positive lymph nodes: 0 positive nodes, 1–3 positive nodes, 4–9 positive nodes, or 10 or more positive nodes; these categories have been shown to have prognostic significance [10]. Statistical analysis of proportions was performed using the χ^2 test, while comparison of groups for continuous variables used analysis of variance.

TABLE I. Relationship Between Tumor Size and Lymph Node Stage in Breast Cancer Patients (n = 283)

	Tumor size		
Nodal stage	T1 (n = 96)	T2 (n = 169)	T3 (n = 18)
0	75.0% (n = 72)	47.3% (n = 80)	16.7% (n = 3)
1–3	16.7% (n = 16)	24.9% (n = 42)	22.2% (n = 4)
4–9	4.2% (n = 4)	14.2% (n = 24)	22.2% (n = 4)
≥10	4.2% (n = 4)	13.6% (n = 23)	38.9% (n = 7)

RESULTS

A total of 362 patients were studied retrospectively. Complete pathological information regarding all 3 levels was available for 302 patients, all of whom were included in this analysis. Patient age ranged from 24 to 89 years (median 56). Modified radical mastectomy was performed in 256 patients (84.8%) and breast conservation in 46 patients (15.2%).

Tumor size data were available for 283 patients, and the median size was 2.0 cm (range 0.2–12.0 cm). Tumor size correlated well with the number of axillary lymph nodes involved (Table I). Evaluation of tumor location revealed that the upper outer quadrant was most commonly involved (62.2%), followed by the upper inner (11.5%), the central (10.5%), the lower outer (9.7%), and the lower inner (6.5%). The median number of lymph nodes removed was 21.0 (range 4–58) per patient. Positive lymph nodes were found in 136 (45%) patients. The pattern of distribution of lymph nodes in each level is shown in Table II.

Patients were analyzed to determine the number of positive nodes present, assuming that these same patients underwent either a level I (only), a level I/II, or a complete (level I/II/III) dissection.

Level I/II vs. Level I Dissection

Assuming that all patients had a level I/II dissection, if the extent of dissection was decreased to level I only, the following changes would have occurred: among the 65 patients with 1–3 positive nodes following a level I/II dissection, 18.5% (12 patients) would be node-negative; among the 36 patients with 4–9 positive nodes, 2.7% (1 patient) would be node-negative and 50% (18 patients) would have 1–3 positive nodes; among the 32 patients with 10 or more positive nodes, downward migration would occur in 17 (53%), most of whom (13/17) would fall into the 4–9 positive node category. If we consider the absolute number of positive lymph nodes, 23.5% of all patients (71/302) would have fewer total positive nodes identified if only a level I dissection was per-

TABLE II. Axillary Lymph Node Distribution in Axillary Contents of Breast Cancer Patients (n= 302)

Level	Dissected nodes/patients median (range)
I	10 (1–35)
II	6 (1–29)
III	4 (1–24)

formed. This represents 53.4% (71/133) of patients with positive nodes.

Level I/II vs. Level I/II/III Dissection

A similar comparison between a level I/II vs. a level I/II/III dissection was undertaken. Among the 169 patients with 0 positive nodes, 1.8% (3 patients) would be upstaged to 1–3 positive nodes while no patients would be upstaged to 4–9 or 10 or more positive nodes. Among the 65 patients with 1–3 positive nodes following level I/II dissection, 4.6% (3 patients) would migrate to the 4–9 category and 1.5% (1 patient) to the 10 or more positive nodes category. Among the 36 patients with 4–9 positive nodes following a level I/II dissection, 16.7% (6 patients) would migrate.

In summary (Table III), if the level of dissection was decreased from level I/II to level I, 15.9% of the patients would have had category migration. With an increase in dissection from level I/II to level I/II/III, 4.3% of the patients would have changed nodal category. This observation was more pronounced in the subgroup of 133 patients with positive nodes. Overall, 36.1% of patients would have changed node categories if only a level I dissection was performed, whereas 9.5% would have changed when the dissection was increased from level I/II to level I/II/III. The category changes resulting from level I vs. level I/II, in comparison to level I/II vs. level I/II/III, was statistically significant ($P < 0.001$).

When considering the absolute number of positive nodes, 16.6% of all patients (50/302) would have had fewer total positive nodes identified if only a level I/II dissection was performed. This represents 36.8% (50/136) of patients with positive nodes.

TABLE III. Changes in Lymph Node Status* Based on Level of Axillary Dissection in Breast Cancer Patients (n = 302)

	Level I/II to level I dissection (% downcategorized)	Level I/II to level I/II/III dissection (% upcategorized)
All patients	15.9	4.3
Patients with ≥1 positive node (n = 133)	36.1	9.5

*Status defined as: 0 positive nodes, 1–3 positive nodes, 4–9 positive nodes, ≥10 positive nodes.

DISCUSSION

Adjuvant chemotherapy has been shown to be effective in the treatment of patients with invasive breast cancer [11]. With the identification of promising chemotherapeutic regimens, attempts are being made to individualize treatments based on patient prognosis. Although various characteristics of the primary tumor correlate with recurrence rates, the presence or absence of metastatic axillary nodes is the most important prognostic factor. Additionally, survival rates have been shown to decrease in proportion to the number of positive axillary nodes [2]. Therefore, most patients are divided into categories of 1–3, 4–9, or 10 or more positive nodes, to help determine prognosis. There is currently a trend to use these different nodal groups to tailor an individual's adjuvant chemotherapy by increasing the intensity of the regimen in patients with a greater number of positive nodes [10]. To this point, dose-intensive chemotherapy with bone marrow transplant was first described in the adjuvant setting among patients with greater than 10 positive nodes [3]. Long-term outcome appears to be superior in these patients when compared to historical controls treated with standard chemotherapy, although randomized trials are ongoing to confirm this observation. Currently, many patients are being offered this treatment both within and outside of a protocol setting. Perloff et al. [12] have reported encouraging results with a dose-intensive (without bone marrow transplant) combination of agents in patients with 4 or more positive nodes. Currently, intergroup protocols are comparing this regimen to dose-intensive therapy with bone marrow/stem cell transplant in this group of patients.

Previous studies have shown that a minimum of 10 nodes need to be dissected for accurate staging [13]. Based on these studies, several cooperative group studies have required that a minimum number of axillary nodes be dissected, not a minimum "level" of dissection. The potential for undercategorization exists when compared to patients undergoing a more thorough dissection. This is illustrated in the present study where a lesser dissection (level I) would have undercategorized approximately 36% of patients with involved nodes. The greatest percentage (36/68 patients, 53%) of undercategorization occurred in patients who would have had 4 or more positive nodes after a level I/II dissection. This is particularly concerning as the intensity of adjuvant chemotherapy is often increased in this group of patients, particularly in the 10 or more positive nodes category. The percentage of node-positive patients who would have been node-negative if a level I dissection were performed was 9.8%, which is consistent with previous reports regarding skip metastases [9,14–17]. Tumor size in this subgroup of patients ranged from 1.5 to 10 cm, with no tumor being

<1 cm. Only 2 patients with negative level I nodes had skip metastasis to level III nodes.

With regard to level I/II/III dissections, node category migration occurred much less frequently, with only 9.5% of node-positive patients being upstaged. Only 3% of node-positive patients with fewer than 4 positive nodes had 4 or more positive nodes identified with a complete node dissection. Furthermore, only 5.2% would have migrated into the 10 or more positive nodes group. This is important in that a complete axillary node dissection can be performed (if indicated) with minimal concern of overcategorizing the patient.

There appears to be a trend toward the use of lymphatic mapping and sentinel lymph node biopsy in patients with clinically negative axillae [18,19]. In the future, lymph node dissection will be performed only in patients with axillary metastases as determined by their sentinel node(s). With the results of the present study in mind, these node-positive patients will require at least a level I/II dissection to assure accurate staging if decisions regarding adjuvant therapy are made based on the number of positive nodes.

In conclusion, increasing the extent of axillary lymph node dissection increases the yield of positive nodes in patients with invasive breast cancer. A level I dissection undercategorizes a large percentage of patients, particularly those with positive nodes. If the number of positive nodes is likely to influence the individual patient's adjuvant therapy, then a standard level I/II dissection should be performed in the clinically negative axilla. Clinical trials requiring a certain number of positive lymph nodes for entry should require at least a standard level I/II axillary dissection and not merely a minimum number of nodes dissected.

REFERENCES

1. Ruffin WK, Stacey-Clear A, Younger J, et al.: Rationale for routine axillary dissection in carcinoma of breast. J Am Coll Surg 1995;180:245–251.
2. Fisher B, Bauer M, Wickerham DL, et al.: Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer: An NSABP update. Cancer 1983;52:1551–1557.
3. Hurd DD, Peters WP: Randomized comparative study of high dose (with autologous bone marrow support) versus low-dose cyclophosphamide, cisplatin, and carmustine as consolidation to adjuvant cyclophosphamide, doxorubicin, and fluorouracil for patients with operable stage I or II breast cancer involving 10 or more axillary lymph nodes (CALBG protocol 9082). Cancer and Leukemia Group B. J Natl Cancer Inst Monogr 1995;19:41–44.
4. National Comprehensive Cancer Network: Update of the NCCN guidelines for treatment of breast cancer. Oncology 1997;11:199–222.
5. International (Ludwig) Breast Cancer Study Group: Prognostic importance of occult axillary lymph node micrometastases from breast cancers. Lancet 1990;335:1565–1568.
6. Morrow M: Axillary dissection: When and how radical. Semin Surg Oncol 1996;12:321–327.
7. Recht A, Houlihan MJ: Axillary lymph nodes and breast cancer: A review. Cancer 1995;76:1491–1512.
8. Burak WE Jr, Goodman PS, Young DC, et al.: Seroma formation following axillary dissection for breast cancer: Risk factors and lack of influence of bovine thrombin. Surg Oncol 1997;64:27–31.
9. Chevinsky A, Ferrara J, James A, et al.: Prospective evaluation of clinical and pathologic detection of axillary metastases in patients with carcinoma of the breast. Surgery 1990;108:612–618.
10. Van Lancker M, Goor C, Sacre R, et al.: Pattern of axillary lymph node metastasis in breast cancer. Am J Clin Oncol 1995;18:267–272.
11. Early Breast Cancer Trialists' Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 1992;339:1–15, 71–85.
12. Perloff M, Norton L, Korzun AH, et al.: Postsurgical adjuvant chemotherapy of stage II breast carcinoma with or without crossover to a non-cross-resistant regimen: A Cancer and Leukemia Group B study. J Clin Oncol 1994;14:1589–1598.
13. Axelsson C, Mouridsen H, Zedeler K, et al.: Axillary dissection of level I and II lymph nodes is important in breast cancer classification [abstract]. Eur J Cancer 1992;28A:1450.
14. Rosen P, Martin M, Kinne D, et al.: Discontinuous or skip metastases in breast carcinoma: Analysis of 1228 axillary dissection. Ann Surg 1983;197:276–283.
15. Veronesi U, Rilke F, Luini A, et al.: Distribution of axillary node metastases by level of invasion. Cancer 1987;59: 682.
16. Pigott J, Nichols R, Maddox W, et al.: Metastases to the upper levels of the axillary nodes in carcinoma of the breast and its implications for nodal sampling procedures. Surg Gynecol Obstet 1984;158:255.
17. Boova R, Bonanni R, Rosato F: Patterns of axillary node involvement in breast cancer. Ann Surg 1982;196:642–644.
18. Guiliano AE, Kirgan DM, Guenther JM, et al.: Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994;220:391–401.
19. Guiliano AE: Sentinel lymphadenectomy in primary breast carcinoma: An alternative to routine axillary dissection. J Surg Oncol 1996;62:75–77.